PART THREE

EPIDEMIOLOGICAL STUDIES OF CORONARY HEART DISEASE

IV. Mortality and Morbidity Statistics in the United States

V. Informative Prospective Studies in Foreign Countries

One of the most significant developments in the management of the patient with coronary heart disease is the prevention of risk factors. The identification of the various risk factors which predispose an individual to develop coronary heart disease has been possible through epidemiological investigations completed in the United States and abroad. The general principle involved in such investigations is to select a group of individuals, in whom to determine the prevalence of coronary heart disease and estimate the extent of smoking, the level of blood pressure, and the cholesterol content, and to assess the genetic, dietetic, psychogenic and socioeconomic factors. In some epidemiologic studies, it has been possible by proper selection of subjects to ascertain the importance of some of these risk factors. Sections IV and V supply the details of the results of analyzing mortality and morbidity statistics.

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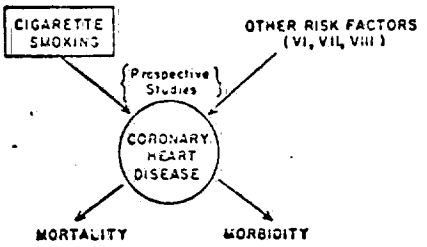
IV. MORTALITY AND MORBIDITY STATISTICS IN THE UNITED STATES



XX PROSPECTIVE STUDIES (IN U.S.A.)

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The most widely quoted reason for the belief that cigarette smoking causes coronary heart disease is that the mortality and morbidity rates are higher for smokers than for nonsmokers. The results of prospective studies of selected groups of individuals form the basis of this statement. The design and conclusions of three early studies relating to mortality caused by coronary heart disease are discussed in this section.

The association between cigarette smoking and coronary heart disease revealed in surveys does not establish a cause and effect relationship. There are other risk factors that are known to occur in individuals with coronary heart disease, which are difficult to exclude. In properly designed prospective studies it has been possible to exclude one of the risk factors, so that the role of cigarette smoking has been identified with some certainty.

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The special studies are discussed in another section (Section V).

The majority of prospective studies are omitted from this section. They appear elsewhere, because the results relate to the importance of risk factors other than cigarette smoking (see Sections VI to VIII). The general articles relating to epidemiology of coronary heart disease are contained in the following list:

List No. 11. Epidemiologic Techniques.

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Additional Bibliographic List No. 11

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IV-A. Initial Prospective Studies

The Surgeon General's Report on "Smoking and Health," which appeared in 1964, contained the results of three prospective studies conducted by the American Cancer Society, the Veterans Adminstration and the Framingham Group respectively. In subsequent years the follow-up of subjects by the last-mentioned group has led to a revision of conclusions based on the results of the two other studies.

Additional prospective studies have been completed in the following countries: Argentina, Australia, Austria, Belgium, Canada, Czechoslovakia, Finland, France, Germany, Great Britain, Greece, India, Iceland, Israel, Italy, Japan, Netherlands, New Zealand, North Africa, Norway, Peru, Philippines, Puerto Rico, South Africa, Sweden, Switzerland, USSR and Yugoslavia. The results are described in Sections IV to VIII and most of the studies are summarized in Table VII-E.

1. American Cancer Society. Beginning in 1951, over 22,000 volunteers interviewed residents in nine states, using a questionnaire prepared for the American Cancer Society. The follow-up study of 187,766 men was performed after 20 months (Hammond and Horn, 1954), after 34 months (Hammond and Horn, 1958a, 1958b), after 44 months on a larger group of 442,094 men (Hammond, 1964), and after 60 months on 804,409 men

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(Hammond and Garfinkel, 1969). Twenty percent of the million men and women enrolled in the study have not been included in these summaries nor in other articles by Hammond (1958, 1960, 1962, 1963, 1968a, 1968b) and by Hammond and Garfinkel (1966, 1969). The results of the survey have been publicized in the US Public Health Reports on "Smoking and Health," which are reproduced and commented upon in Section XIV. The conclusions are once more noted here for comparison with those from other prospective studies.

a. High incidence of death from coronary heart disease. After 44 months 2,665 men died, the cause of death in 1,388 (52.1%) being coronary artery disease. After 60 months the deaths due to coronary artery disease totaled 14,819.

b. Influence of smoking. The death rate from coronary artery disease was directly related to the amount of cigarette smoking by the individual. Among men in all age groups and women under the age of 70, coronary heart disease death rates were much higher in cigarette smokers than in nonsmokers. The highest mortality rate of 5.6% was for the group of men who smoked 40 or more cigarettes a day as compared with the nonsmokers. Within groups of men who were alike in respect of age, relative weight and blood pressure, coronary heart disease death rates increased with the amount of cigarettes smoked.

c. Risk factors. In an analysis of risk factors, death rates for coronary heart disease were combined with those for stroke and aortic

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aneurysm. The combination of diabetes and a history of high blood pressure is predictive of extremely high death rates. The combination of obesity and cigarette smoking is predictive of high death rates, and that of heavy smoking and a history of high blood pressure of even higher death rates. The predictive death rates for cigarette smoking alone has not been calculated.

2. Veterans Administration. In 1954, the causes of death among policyholders of US Government life insurance were analyzed. The mortality experience of 200,000 policyholders for 2 years was summarized by Dorn (1958), 1959). The ratio of men dying of cardiovascular disease was 1.40 for smokers as compared with nonsmokers.

3. Framingham Heart Disease Epidemiology Study. In 1950 an epidemiologic study was begun in Framingham, Mass., and observations have been made on 5,128 adults, who were examined biennially by physicians for a period of up to 16 years. The conclusions reached in follow-up studies made at intervals of an increasing number of years are noted below.

Four-year follow-up. There was variability of attack rates, so that it was not possible to make generalizations on morbidity and mortality in heart disease. The data suggest that the association of heart disease with smoking is not as strong as that shown with elevated blood pressure, weight and cholesterol (Dawber, et al., 1957).

Six-year follow-up. Smoking was associated with an increased incidence of nonfatal myocardial infarction and of death from coronary heart disease in men aged 45-62. It was not associated with an increased

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incidence of angina pectoris. Cholesterol levels were higher among cigarette smokers than among nonsmokers and were also higher among those who had smoked and stopped than among those who had never smoked. Neither weight not blood pressure showed a similar association with smoking (Dawber et al., 1959).

Eight-year follow-up. Heavy cigarette smokers experienced a threefold increase in the incidence of myocardial infarction and in death from all causes as compared with nonsmokers, pipe and cigar smokers and former cigarette smokers. Cigarette smoking is apparently unrelated to the incidence of angina pectoris. Former smokers and cigar and pipe smokers have morbidity and mortality experiences similar to those of individuals who have never smoked (Kagan et al., 1962).

Ten-year follow-up. Observations in the Framingham Study of 5,128 subjects for periods of ten years indicate that many personal characteristics are related to the development of coronary heart disease. The major risks appear to be elevation of the serum cholesterol level and elevation of blood pressure, though there are several other contributing factors. Combinations of factors further augment the risk and characterize a highly susceptible subject. Recommended beneficial changes in these factors appear to be warranted, particularly in persons exhibiting one or more high-risk traits. (Dawber and Kannel, 1962a, 1962b; Dawber et al., 1962, 1963; Kannel et al., 1962b; Revotskie et al., 1962; Dawber, 1963.)

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Twelve-year follow-up. After a decade, every 10th man and every 20th woman developed coronary heart disease; in the men it resulted chiefly in myocardial infarction or sudden death, in the women chiefly in angina pectoris.

In order to assess the importance of several risk factors, the incidence of coronary heart disease in a group with a definite value (e.g., cholesterol 210-220) (observed cases) was divided by the incidence of coronary heart disease in a group of the same age and sex distribution but with a random cholesterol value (expected cases). The figure resulting from this division x 100, the morbidity ratio, varied with the following risk factors:

		MR
Cholesterol	<200 mg %	55
	>260 mg %	178
Systolic blood pressure	<120 mm Hg	45
	>180 mm Hg	178
Vital capacity	>4 litres	81
	<3 litres	128
ECG anomalies	none	91
	present	203
Overweight	none	50
	present	241*
Cigarette smoking	nonsmoker	69
	20 cgs/day	158

* angina pectoris only

(Dawber, 1963; Dawber et al., 1963a, 1963b; Friedman et al., 1967; Kagan et al., 1963; Kannel et al., 1965, 1966, 1967; Oberwittler, 1968; Truett et al., 1967.)

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Fourteen-year follow-up. Risk of every manifestation of coronary heart disease, including angina, coronary insufficiency, myocardial infarction and sudden death, was distinctly and impressively related to the antecedent level of both systolic and diastolic blood pressure. Risk was not solely related to "hypertension" but was proportional to the level of the blood pressure—even at nonhypertensive pressures—from the lowest to the highest recorded. Also, risk appeared to be related to casual as well as mean basal pressures.

Risk of coronary heart disease over 14 years was examined prospectively in 2,845 women according to their antecedent cholesterol and lipoprotein status. In women under 50 years of age high cholesterol values, as in men, were associated with an increased risk of coronary heart disease and this was true even when adjustment made for concomitant pre-beta lipoprotein and other factors related both to coronary risk and to blood lipid content. In women over 50, however, triglyceride-rich pre-beta lipoprotein was superior to cholesterol for identifying potential coronary cases. Risk of coronary heart disease in women is better estimated by cholesterol under the age of 50 and by pre-beta lipoprotein, or by inference endogenous triglyceride, after that age. (Gordon and Kannel, 1971; Kannel, 1970; Kannel and Castelli, 1972; Kannel and McNamara, 1964; Kannel et al., 1969.)

Sixteen-year follow-up. Cigarette smoking appears to be one of the important risk factors among men for coronary heart disease and cerebrovascular and peripheral vascular disease. For women it is important

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only as a factor related to intermittent claudication. Cigarette smoking bears little relation to angina pectoris. Of all the key factors, cigarette smoking is the only one whose relative role is enhanced in multivariate analysis—that is, when the other risk factors are considered at the same time. From a biological point of view, it is conceivable that the presence of other atherosclerotic factors is a precondition for cigarette smoking to affect atherosclerotic outcomes, but there is nothing in the statistical analysis bearing on this question (Kannel and Gordon, 1971a, 1971b).

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IV-B. Other Prospective Studies

Fifteen additional prospective studies have been completed in the United States. The design and results are summarized in Table IV-B. The important conclusions are as follows:

1. Myocardial infarction. All the studies show a high incidence of smoking in patients who develop or die from myocardial infarction.

2. Angina pectoris. Like the Framingham Study, the prospective studies reported by the Albany Group and the Western Collaborative Group did not reveal an association between cigarette smoking and angina pectoris. It is unfortunate that most prospective studies have pooled angina pectoris and myocardial infarction into a single disease entity, so that it was not possible to differentiate their respective relationships to smoking.

3. Other risk factors. The prospective studies indicate that, in patients with coronary heart disease, other risk factors are as frequent as cigarette smoking, if not more so. The factors which have been identified include blood pressure, blood cholesterol levels, diet, physical activity, race and behavior patterns.

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Table IV-B. Later prospective studies

Investigation and Design	Affect of Cigarette Smoking	Other Risk Factors
New York Health Insurance Plan 110,000 persons questioned from 1961 to 1964. Frank 1968 Frank et al.; 1963, 1966 Shapiro et al.; 1965, 1969, 1963 Weinblatt et al.; 1968a, 1968b	Male cigarette smokers have twice the risk of sustaining a first myocardial infarction shown by nonsmokers. Cigarette smoking is also associated with a doubling in risk for angina among men. Women who smoke cigarettes have twice the incidence rate of first infarction shown by nonsmokers; no difference in the risk for angina.	Physical activity. Body weight 15% or more above average. Race.
Albany, New York 1,838 men examined 1953 to 1955. Doyle et al.; 1959, 1962, 1964	Heavy cigarette smokers experience a similar risk of myocardial infarction compared with nonsmokers. Increased risk or death was associated with cigarette smoking in all combinations of high and low systolic blood pressure and cholesterol levels. Risk of angina pectoris is unrelated to tobacco habit.	
Pennsylvania and Massachusetts College Graduates 1,146 coronary decedents compared with 2,292 classmates. Paffenberger et al., 1966 Paffenberger and Wing, 1969 Thorne et al., 1968	Cigarette smoking and nonparticipation of sports were associated with 50% increase of coronary death.	Systolic blood pressure shorter body stature.
Philadelphia Periodic Health 350 examined who died compared with their living counterparts. Schor et al., 1964a, 1964b	Among those who died of undetermined coronary heart disease, the only finding that clearly discriminated between them and living counterparts was heavy smoking.	
Evans County, Georgia 3109 persons examined 1960-1962 Cassel 1971a, 1971b Garrison et al., 1966 McDonough et al., 1965a, 1965b Kleinbaum et al., 1971	Cigarette smoking could not explain the difference in prevalence of coronary heart disease between Negroes and whites.	Blood cholesterol level. Physical activiy. Race.

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Investigation and Design	Affect of Cigarette Smoking	Other Risk Factors
Teumseh, Michigan 8,641 persons around 1956-1960. Chiang et al.; 1969, 1970 Epstein 1967 Epstein et al., 1965 Higgins and Kjelsberg 1967 Higgins and Keller 1970	Smoking has no influence on prevalence of coronary heart disease on initial examination of subjects. Smokers have lower weight, lower diastolic blood pressure and serum uric acid. Incidence of sudden death in persons with antecedent ventricular premature systoles are independent of smoking habits.	
Chicago Board of Health 1,329 men observed for 9 years. Berkson et al., 1960 Kjelsberg and Stamler 1960 Stamler 1964a, 1964b, 1968, Shekelle et al., 1969	Cigarette smoking as a sole factor is associated with a marked increase in risk. Mortality rate for myocardial infarction is 10 times higher than for low-risk groups.	Hypercholesterolemia Hypertension.
Western Electric Co. of Chicago 1,989 men observed for 4 years Paul et al., 1963	Association of cigarette smoking, most of adult life with subsequent development of coronary disease	Elevated blood cholesterol Use of coffee.
University of Minnesota 11,132 for 5 years. 279 for 20 years. Keys et al.; 1971, 1972	Smoking habit and body weight seemed unimportant in predicting heart disease	Age. Systolic pressure. Serum cholesterol. Diet.
North Dakota State Dept. 1,886 males interviewed. Zukel et al. 1959	Higher incidence of coronary heart disease among smokers.	
Navajo Indian 508 adults for 6 years. Fulmer and Roberts 1963	Smoking rare; low incidence of coronary heart disease.	Diet.
Southwestern American Indians 15,905 adults from 1957 to 1966. Sievers 1967, 1968	Cigarette smoking rare; low incidence of coronary heart disease.	
Western Collaboration Group Study 3,000 subjects since 1960. Barron 1968 Jenkins et al.; 1968a, 1968b Rosenman 1968 Rosenman et al.; 1966, 1967a, b, c; 1968, 1970	Fatal cases have higher frequency of smoking; silent infarction or angina pectoris not associated with smoking.	Overt behavior pattern. Hypertension. Abnormal lipoprotein pattern.

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Table IV-B. (continued)

Investigation and Design	Affect of Cigarette Smoking	Other Risk Factors
California Health Survey 68,153 men from 1954 - 1957; death record in 1962. Borhani et al., 1965 Buechley et al., 1958 Drake, et al., 1957 Weir and Dunn 1970.	Increasing risk of heart disease with greater amount of smoking.	
Seventh-Day Adventists 564 patient records in hospitals. Lemon and Walden 1966 Wynder 1958 Wynder et al., 1959	Smoking plays a role in precipitating coronary artery disease in individuals less than 60 years old; incidence less frequent.	

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IV-C. Critique of Mortality Statistics

In accepting mortality statistics of coronary heart disease there are five considerations to support the thesis that cigarette smoking is one of the important risk factors. They are as follows:

1. Death certificate. The reliance on the death certificate to identify individuals who died of coronary heart disease can be criticized as to its accuracy (Beadenkopf et al., 1963). In 1940 Swartout and Webster reported that with patients hospitalized for less than 48 hours before death there were approximately twice as many discrepancies between the designations of the cause of death and the findings of subsequent autopsies as with patients having longer lengths of medical attendance. Moriyama et al. (1958) and Moriyama (1963) suggested that a strong association between quality of diagnosis and length of attendance might be expected, although for technical reasons their findings on this point were inconclusive. Markush and Schaaf (1966) analyzed 405 death certificates and noted that short attendance by the death certifier was associated with cigarette smoking by the deceased. The pattern relating short attendance to smoking suggests that death certificate diagnoses for cigarette smokers may not be comparable with the diagnoses for nonsmokers. The accuracy of epidemiologic studies conducted by the American Cancer Society may be questioned, since the record of occurrence of heart disease was derived from notation on the death certificate.

2. Combining individual diseases into one group. The International

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List of Causes of Death includes the following types of coronary heart disease:

420.0 Arteriosclerotic heart disease, so described (with or without mention of coronary disease or angina pectoris).

420.1 Heart disease specified as involving coronary arteries.

420.2 Angina pectoris without mention of coronary disease.

In practice, the attending physician can make a distinction between angina pectoris and myocardial infarction, so that it is possible to differentiate between the two clinical entities. Most prospective studies pool both into one single entity of "coronary heart disease," and, when the two are differentiated, the association with cigarette smoking is not the same for both. The mortality statistics show an increasing trend toward death from coronary heart disease (Riesman and Harris, 1934; Lew, 1957; Campbell, 1963a, 1963b). With the current practice of using the designation coronary heart disease it has not been possible to state whether this increasing trend related to either angina pectoris or myocardial infarction or to both (Beadenkopf, 1963).

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3. Pooling of geographical areas and occupational groups. The American Cancer Society survey combines geographical areas. There are striking geographic variations in death rates for coronary heart disease (Friedman, 1967). One extreme example was a group of 11,000 employees of cigarette factories, who were heavy smokers, but the 14-year mortality rate resulting from heart disease and other diseases was below that

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reported by the American Cancer Society (Cohen and Heimann, 1962).

4. Participation of risk factors. In prospective studies several risk factors, including cigarette smoking, have been shown to occur in patients with coronary heart disease (Hilleboe, 1957; Spain, 1960; Acheson, 1962; Epstein, 1965; Cornfield and Mitchell, 1969; Hall et al., 1972). The techniques of retrospective studies are varied and have not been standardized. The shortcomings of some of these technical methods have been discussed by Mulcahy (1967) and Weinstein et al. (1964).

5. Etiology of coronary heart disease. Although several risk factors have been identified, there is a possibility that not all have been determined. It was only recently that phenformin, an antidiabetic drug in use for 20 years, was recognized as a cause of coronary heart disease (Tzagournis et al., 1972). The low incidence of coronary heart disease among Seventh Day Adventists has been explained largely by the fact that they are nonsmokers (Lemon and Kuzma, 1969). The possibility that members of the families of this religious order may have inherited a trait that renders them resistant to coronary heart disease has not been excluded. The mortality encountered in alcoholics has been reported to be associated with a high incidence of smoking (Rankin et al., 1969). Excessive drinkers are usually heavy smokers (Bailey et al., 1969). The problems in identifying other risk factors have been reviewed by Syme (1967).

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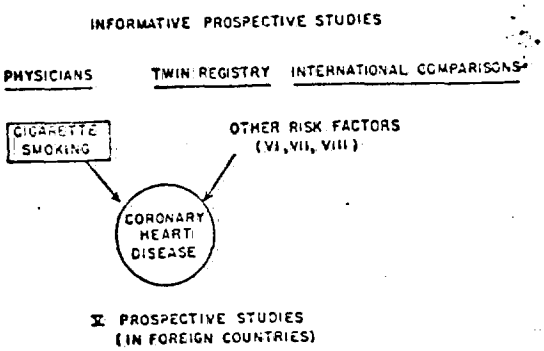
V. INFORMATIVE PROSPECTIVE STUDIES IN FOREIGN COUNTRIES



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The prospective studies in foreign countries are essentially similar to those in the United States, which are reviewed in Section IV. However, important modifications have been made in the design of the foreign studies. By the selction of one occupation, i.e., British medical practice, it has been possible to assure a uniform accuracy of answers to a questionnaire. By searching for twins, the importance of inherited constitutional factors has been demonstrated through comparison of the representatives of one occupational group in several countries, the risk factors relative to cigarette smoking in the causation of coronary heart disease have been elucidated. A selection of such prospective studies is included in this section. Other studies are described in Sections VI to VIII in the discussion of individual risk factors. The general articles on epidemiologic techniques are listed as follows:

List No. 12. Epidemiologic studies in foreign countries.

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V-A. Mortality from Coronary Heart Disease of Physicians

Although coronary heart disease had been known to be a "disease of doctors," the first study of its incidence among physicians was reported in 1937 by Smith from the United States. He compared the incidence of coronary sclerosis among physicians, bankers, lawyers, clergymen, laborers and farmers in the clientele of the Mayo Clinic, examining the consecutive clinical records of about 300 persons in each occupational group. The incidence was 10.7% among physicians, whereas in other groups it was less than half that rate, ranging from 2.5 to 5.3%.

A survey of 59,600 British physicians was initiated in October 1951. Questionnaires were sent to them initially and at various times during a period of 10 years. The cause of death of doctors who had replied to the questionnaire and who subsequently died was obtained from the death certificate. The mortality statistics were reported from a follow-up after 29 months (Doll and Hill, 1954), 53 months (Doll and Hill, 1956) and 10 years (Doll and Hill, 1964a, 1964b, 1966).

In the deaths attributed to coronary heart disease or cerebrovascular accident the presence of hypertension was considered. There was no association of smoking habits with the 138 deaths in which hypertension was the primary cause, with the 143 cerebrovascular accidents, nor with the 89 coronary deaths in which hypertension was also mentioned. The only cardiovascular cause of mortality to show any association with smoking habits is coronary disease unrelated to hypertension, and here the

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differences in rates are not marked. The death rate for all smokers (4.08 per 1,000) is 23% higher than that for nonsmokers (3.31) and this excess appears to be limited to the cigarette smokers (4.39). There is no clear gradient with the number of cigarettes smoked but the highest mortality is found among the heaviest smokers. A rising gradient of mortality from nonsmokers to heavy cigarette smokers is clearly present at ages under 65, doubtful at ages 65 to 74 and absent at age 75 years and over. The death rates per 1,000 are as follows:

		Smokers with a daily consumption of:		
Age	Nonsmokers	1-14	15-24	25+ cigarettes
35 to 44	0.11	0.41	0.49	1.50
45 to 54	1.12	1.66	3.40	2.73
55 to 64	4.90	6.81	7.03	8.81
65 to 74	10.83	16.44	13.04	17.59
75 to 84	21.20	21.22	15.04	17.30
85 +	32.35	33.06	58.54	—
all ages	3.31	4.36	4.28	4.97

A second survey of physicians was made, comprising 7,000 British medical practitioners. The respective incidence of coronary heart disease was compared during three periods, namely, 1947 to 1950, 1957 to 1960, and 1961 to 1965 (Meade et al., 1968). The incidence of the first attack of coronary heart disease altered little in the first two periods but increased in the third period. The increase was particularly marked for the 45 to 54 year age group. Although data regarding the smoking habits of doctors were not solicited in the survey, the authors related their results to changes in smoking habits.

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In the United States, a number of surveys have been conducted to determine the association of coronary heart disease. Russek (1960, 1961) noted a high incidence (70%) of smoking among 100 physicians with coronary heart disease as compared with a control group (35%). In a survey of 12,000 men in 14 occupational groups, including physicians, Russek (1965) noted that the incidence of coronary heart disease showed a marked gradient which was unassociated with heredity or diet but strikingly related to the stressfulness of occupational activity. Smoking was not only found to be stress-related but also statistically correlated with the reported frequency of ischemic heart disease. A paradox was noted which casts doubt upon the alleged role of smoking in the genesis of coronary heart disease and adds further emphasis to the probable influence of emotional factors in its causation. Coronary disease was more prevalent among nonsmokers (6.54%) than among exsmokers (2.34%).

Rogers (1965) noted that there was no improvement in mortality from heart attacks among physicians from 1954 to 1964 even though there had been a sharp decline in cigarette smoking during this period. Snegireff and Lombard (1963) recorded the smoking habits of Massachusetts physicians and the death rate among them but did not identify coronary deaths. The mortality rates of physicians in several countries were compared by King (1970) but their smoking habits were not noted. The association between smoking and coronary heart disease has not been investigated in countries other than Great Britain and the United States.

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V-B. Smoking Habits of Twins

The twin registry was established in Sweden to determine whether a constitutional factor predisposes a person to excessive smoking and to diseases. A comparison between the smoking habits of 59 pairs of adult monozygotic twins and 59 pairs of adult dizygotic twins showed significantly greater concordance within the monozygotic pairs (Friberg et al., 1959). These results indicate the importance of the genotype in regard to smoking habits.

The relation of heredity to coronary heart disease in 193 twins was examined by Lundman (1966). The series was small, so that it was impossible to draw definitive conclusions regarding heredity and the disease. In a larger series of 9,168 twin pairs, the studies of a population of first-born twins revealed an increased incidence of angina of 1.50 among male smokers in urbanized areas as compared with smokers in rural districts. No difference between areas was found with respect to nonsmokers; therefore the combination of smoking and the urban factor seems to be associated with the symptom of angina. Smoking as such does not cause angina pectoris, since in smoking-discordant twin pairs there was no difference in morbidity (Cederlöf et al., 1966a, 1966b, 1966c). There was a higher concordance rate among monozygotic twin pairs with regard to angina pectoris than among dizygotic twin pairs, which suggests the existence of a genetic predisposition for the development of angina pectoris (Cederlöf et al., 1967). In 32 pairs of identical male twins with discordant coronary heart disease,

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the severity of coronary heart disease related to psychosocial factors but not to smoking, obesity or blood cholesterol levels (Liljefors, 1970; Liljefors and Rahe, 1970; Lundman et al., 1971). The other results of twin-registry relate to the records of mortality (Friberg et al., 1970; Cederlöf et al., 1970) and of respiratory symptoms (Cederlöf et al., 1967).

An International Symposium (1971) was held in Puerto Rico to discuss plans for twin registries in several countries. In Denmark, analysis or 1,584 pairs of twins revealed a slight and nonsignificant tendency toward coronary infarction to be associated with heavy smoking. Angina pectoris was significantly more frequent in cotwins with a higher significant consumption of tobacco than in those who consumed less tobacco or none at all (Hauge et al., 1970). In 16,000 pairs collected in the United States, the statistics showed an association between smoking and angina. However, it is questionable whether this excess morbidity is causal, since it was not possible to reproduce the association when studying monozygotic smoking discordant twin-pairs (Cederlöf et al., 1969). The appearance of coronary heart disease in identical twins strongly suggest a greater influence linked through the monozygotic inheritance (Sidd et al., 1966; Douglas and Arkun, 1969).

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V-C. International Comparisons of Mortality Statistics

The World Health Organization (1963) has published the cardiovascular disease mortality for various countries. Several comparisons have been made between countries to determine the relationship of smoking to coronary heart disease.

1. Geographic variation in cigarette consumption. Mulcahy et al. (1970) noted a significant positive association between cigarette consumption and coronary heart disease mortality in 21 countries, including the United States, Great Britain, Sweden and Finland. In 15 of these countries, there was a significant association between total cigarette consumption and excess female/male expectation of life, which may be accounted for by the documented or assumed heavier smoking by males. The authors interpreted their results as consistent with, but not proof of, the hypothesis that cigarette smoking is a significant risk factor in coronary heart disease mortality.

2. Importance of blood pressure. The other comparisons considered risk factors not related to smoking in patients with coronary heart disease. In 600 middle-aged men similarly employed in England and in the Eastern United States, the prevalence of chest pain and electrocardiographic evidence of cardiac ischemia are significantly more common among the American men, particularly those over 50 years of age (Reid et al., 1967). The higher blood pressure observed in Americans is readily explained by their greater body weight and skinfold thickness. Although there are differences in smoking habits, it is suggested that factors associated with

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excessive adiposity of the Americans are the more likely explanations of their adverse experience in cardiac disease.

Clerical workers drawn from 5 European countries were examined in a collaborative study (Rose et al., 1968). The results of a standard questionnaire sent to 4,522 subjects and of electrocardiograms in some cases indicate a high prevalence of coronary heart disease in all countries. Cigarette smoking was not associated with prevalence of this disease. An elevated blood pressure was the most consistent risk factor. Higgins et al. (1972) compared miners in the United States with those in Great Britain and concluded that blood pressure, rather than weight and smoking, has the most striking association with prevalence of coronary heart disease. The international comparisons of Reid et al. (1966) and of Stocks (1969) did not include a comparison of blood pressure, cigarette smoking and mortality from coronary heart disease.

3. Importance of blood cholesterol level. The epidemiology of coronary heart disease in 7 countries has been reported by Keys et al. (1970) and have publishe supplements to the Acta Medica Scandinavica and to Circulation. The most consistent theme of the reports is that inhabitants of the geographic areas characterized by serum cholesterol values of approximately 200 mg % have a relative immunity to coronary atherosclerosis and its complications. Cigarette smoking clearly appeared to be a significant risk factor in American railroad employees but this was less certain in the other countries (Paul, 1970).

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V. INFORMATIVE PROSPECTIVE STUDIES IN FOREIGN COUNTRIES

C. International Comparisons of Mortality Statistics.

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PART FOUR

RISK FACTORS FOR CORONARY HEART DISEASE

VI. Fixed Risk Factors

VII. Preventable Risk Factors

VIII. Preventable Risk Factors Probably Influenced by Cigarette Smoking

In recent years, the statistics of mortality and morbidity have been cited as supporting the hypothesis that cigarette smoking causes coronary heart disease. The major objection to the use of statistics is that the pathogenesis of coronary heart disease is of a complex nature. There are several risk factors, including cigarette smoking, which are known to predispose individuals to develop coronary heart disease. However, the importance of risk factors relative to cigarette smoking has not been determined.

For the purpose of this review, the risk factors are divided into two groups comprising preventable and nonpreventable or fixed risk factors. The former group has been further divided into those that are probably influenced by cigarette smoking and those that are not. Since most of the literature cited in these sections pertains to the epidemiology of coronary heart disease, the geographical location of each investigation is specified.

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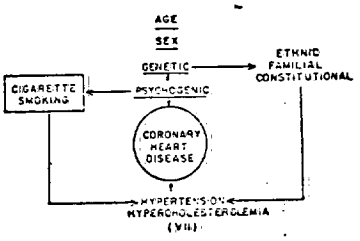
VI. FIXED RISK FACTORS



XI FIXED RISK FACTORS

A. Age and the Prevalence of Coronary Heart Disease------- 122
B. Sex as a Risk Factor---------- 126
C. Genetic Factors------------- 129
D. Psychogenic Factors---------- 134

The prevalence of coronary heart disease is determined by age, sex, and genetic and psychogenic factors. The last two of these are interrelated in that the behavioral pattern of a coronary patient is actually an inherited trait, but it may also be influenced by socioeconomic conditions, discussed in Section VII. The list of genetic factors includes the ethnic group, familial predisposition, and constitutional features. An individual who inherits the predisposition to coronary heart disease is more likely to acquire the smoking habit. The predisposition to develop hypertension and hypercholesterolemia can also be inherited but these are discussed in Section VII, since both factors can be either controlled or prevented.

The articles relating to fixed risk factors are in the following additional bibliographic lists:

List No. 13. Risk factors in coronary heart disease.
List No. 14. Risk factors in coronary heart disease in the young adult.
List No. 15. Stress and psychogenic factors in coronary heart disease.

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VI-A. Age and the Prevalence of Coronary Heart Disease

Coronary heart disease appears more frequently in the elderly (Thould, 1965). It was stated in Section IV that the association between cigarette smoking and coronary deaths is more conspicuous in the younger age group (see also bibliographic List No. 14). This is supported further by the examination of patients under 40 years of age who develop coronary heart disease. Of the 18 investigations listed in Table VI-A, 8 show an incidence of smoking exceeding 90 %. There are 10 reports in which the patients are either nonsmokers or smokers who are less numerous among the controls.

The high incidence of smoking among the young patients developing coronary heart disease does not necessarily mean that cigarette smoking is the cause. The following risk factors have been identified as equally important in the pathogenesis of the heart disease: family history (White, 1935; Roth and Pepe, 1957); lack of exercise (White, 1957); increased blood cholesterol (Gertler et al., 1951; Hatch et al., 1966; Walker and Gregoratos, 1967; Bahl et al., 1970); imparied glucose tolerance (Hatch et al., 1966); mesomorphic body build (Gertler et al., 1951; Roth and Pepe, 1957) Nanda, 1967); obesity (Walker and Gregoratos, 1967); and nervousness (Roth et al., 1967).

There is no survey which indicates that cigarette smoking is the only important risk factor.

(Table VI-A appears on the next page.)

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Table VI-A. Controlled retrospective studies of young male adults with coronary heart disease

Country Investigator	Coronary Heart Disease No.	 % Smokers	Control % Smokers
United States			
White (1935)	28	100	
Gertler et al., (1951)	100	81	76
Roth and Pepe (1957)	20	90	
Hatch et al. (1966)	24	96	70
Roth et al. (1967)	53	87	
Walker and Gregoratos (1967)	100	87	
Sidd et al. (1970)	1	0	
Nizet and Robertson (1971)	1	0	
Czechoslovakia			
Jakuszewska (1969)	22	45	
France			
Bolens and Ferrero (1967)	1	100	
Germany			
Dörken (1967, 1968)	205	99	82
Gsell (1966)	2	100	
Hungary			
Lukl and Weinberg (1963)	31	86	
India			
Mukerjee (1968)	15	33	63
Bahl et al. (1970)	29	52	68
Mexico			
Moleiro and Medina Briceno (1968)	84	74	
Estandia Cano et al., (1971)	84	94	
Poland			
Ciświcka - Sznajderman et al. (1971)	60	97	75

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VI-B. Sex as a Risk Factor

The importance of coronary heart disease as a cause of death in women has been overshadowed by the magnititude of this disease in men. The male to female ratios of coronary deaths range from 2 to 6. In recent years, the total number of females dying from coronary heart disease has been slowly increasing. One cause is the earlier onset of the menarche and of the menopause compared with several decades ago (Mills, 1937). The female gonadal hormone is believed to retard coronary heart disease, and, when estrogen production subsides following the menopause, there is a sharp increase in mortality (Furman, 1968; Klink, 1970; Paulussen, 1970).

Another explanation proposed for the increasing incidence of coronary heart disease is the rising consumption of cigarettes among women (Hartroft, 1956). An examination of women who develop coronary heart disease indicates that there is a wide range of incidence of smoking, from 20 to 90 % (TableVI-B). In the same surveys, the following risk factors have been identified as prevalent in female patients: hypertension (James et al., 1955; Mulcahy et al., 1967a, 1967b; Dörken, 1967), hypercholesterolemia (Oliver, 1971), diabetes (James et al., 1955) and overt behavior pattern (Rosenman and Friedman, 1961). It has not been possible to assess the importance of these risk factors relative to cigarette smoking in females who suffer from coronary heart disease.

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Table VI-B. Controlled retrospective studies of female adults with coronary heart disease

Country Investigator	Coronary Heart Disease No.	 % Smokers	Control % Smokers
United States			
James et al. (1955)	112	20	
Eliot and Bratt (1969)	15	53	7
Rosenman and Friedman (1961)	29	38	45
France			
Jouve et al. (1966)	330	24	14
Germany			
Dörken (1967)	20	90	33
Wink and Hager (1972)	273	60	4
Great Britain			
Mulcahy et al. (1967a) (1967b)	100	63	46
Kenya			
OJiambo (1968)	1	0	

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VI-C. Genetic Factors

The importance of genetic factors in the causation of coronary heart disease has become apparent by the analysis of males of 65 years of age or older who do not suffer from the disease (Brown and Ritzman, 1967). The smoking habits of 133 such individuals compared with those of 100 control patients with heart disease were as follows:

Males without heart disease	Controls with heart disease
40 % nonsmokers	31 % nonsmokers
49 % smokers, inhalers	61 % smokers, inhalers
11 % smokers, noninhalers	8 % smokers, noninhalers
9,550 average pack-years	11,201 average pack-years

It was further noted by Brown and Ritzman that the difference in pack-years between the two groups was not statistically significant. The following factors were found to be associated with this absence: moderate eating habits, regular physical exercise, lack of concern with social status, normal serum total cholesterol levels, and no family history of heart disease. The last three factors can properly be identified as genetic and are discussed in this section.

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Before the individual genetic factors are discussed, it is pertinent to mention other types of investigations relating to the problem. A review of factors relevant to a low prevalence of coronary heart disease in population groups throughout the world failed to identify a consistent pattern of racial or other risk factors (Bruhn and Wolf, 1970). However, twin

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registries established in Sweden and other countries have proven the importance of genotypes in the prevalence of coronary heart disease (see Section V-B). A similar conclusion holds for the hypertension and arteriosclerosis in monozygotic twins (Liebegott, 1965).

1. Ethnic groups. Several reports cited elsewhere in this review indicate the predominance of coronary heart disease in white males compared with black men. The prospective survey conducted by Cassel et al. (1971) in Georgia revealed that, of 143 new cases of coronary heart disease occurring in a seven-year period, the adjusted incidence rate/1,000 was 83 for white and 24 for black males. The females did not show a significant difference, the rate/1,000 being 38 for whites and 34 for blacks.

The South African Bantu and the people of India are less prone to develop coronary heart disease (see review by Walker, 1969).

2. Family history. The hypothesis that coronary heart disease is at least in part a hereditary disorder is based on prevalence studies (Russek, 1959; Meigs, 1966). It has been noted that, by interviewing students, the greates proportion of affected persons was always found among the offspring of 2 affected parents and the smallest among the offspring of 2 unaffected parents (Thomas, 1959). The importance of an inherited predisposition was arrived at by interviewing 75 survivors of myocardial infarction (Rose, 1964), by correlating absenteeism with reported causes of parental death in a group of 98 men, and in a comparison of death rates of individuals with longevity of their parents and grandparents (Hammond et al., 1971).

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In the last-mentioned study, the death rates from coronary heart disease, hypertensive heart disease and stroke were found to be considerably higher among short-lived parents than among subjects with long-lived parents. This was found to be the case for coronary heart disease among men without a history of high blood pressure or diabetes, who were not seriously overweight, who took some exercise and who did not smoke cigarettes regularly.

A comparison of siblings in Boston and Ireland indicated that physical activity, way of life and meal patterns may be associated with the difference in death rates for cases of coronary heart disease in the United States and Ireland (Trulson et al., 1964). The familial history of the subjects was not examined. However, the smoking habits were noted to be similar, i.e., 36 % of Boston samples and 28 % of men in Ireland smoked more than one package of cigarettes daily. The higher death rate in the United States cannot be attributed to smoking.

3. Constitutional factors. The coronary-prone individual is characterized by amphometric features and biochemical changes in the blood. Among the latter, the serum cholesterol level has the highest correlation with coronary heart disease (Gertler et al., 1959). Details of this risk factor are discussed in Section VIII-C. The genetic hypothesis as it relates to coronary heart disease has been reviewed by Thomas (1968).

The relationship of cigarette smoking to constitution has been examined by Damon (1961). Among 167 adult male factory workers of

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Neapolitan parentage but of American birth or upbringing, the lean men smoked significantly more than the fat ones. Smoking was not associated with morphological masculinity. In a study of American-born college students by Baer (1966), heavy smokers were significantly taller than light smokers, former smokers and nonsmokers. The relevance of these observations to coronary heart disease need to be investigated.

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VI-D. Psychogenic Factors

The individual who is prone to develop coronary heart disease has a personality different from those of others. Several review articles have appeared describing the psychologic makeup of patients who have coronary heart disease (see List No. 15). A distinct behavior pattern accompanied by biochemical derangements has been identified in coronary patients by Friedman and Rosenman (1959, 1971), Friedman et al. (1960, 1970) and Rosenman (1971).

It has been suggested that the high incidence of coronary heart disease among smokers can be attributed to one common cause. The personality of the smoker has been examined and found to be different from that of the nonsmokers (McArthur et al., 1958; Lilienfeld, 1959; Eysenck et al., 1960; Matarazzo and Saslow, 1960; Salber and MacMahon, 1961; Dimond, 1964; Thomas et al., 1970). Russek (1964) has used the smoking pattern in the individual to provide an index by which emotional tensions may be relatively assessed. The smoking behavior of offsprings of patients with heart disease has been analyzed (Rappaport et al., 1968). If follow-up studies of offsprings are extended to determine the appearance of heart disease, then the genotype similarities between smokers and nonsmokers will become apparent.

The occurence of psychogenic factors in coronary patients is accompanied by other risk factors, particularly hypercholesterolemia

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(Teculescu et al., 1972; Segers and Mertens, 1972). An estimation of multivariate logistic risk function including personality and smoking habits has been attempted by Halperin et al. (1971).

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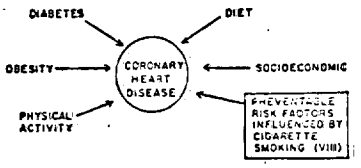

XII PREVENTABLE RISK FACTORS (NOT INFLUENCED BY SMOKING)

A. Physical Activity and Exercise- 148
B. Obesity---------- 151
C. Diabetes Mellitus and Sucrose Intake---------- 153
D. Diet and Coronary Heart Disease---------- 157
E. Socioeconomic Factors------- 160

The preventable risk factors are discussed in this section separately from those listed in Section VIII. The two groups can be differentiated by cigarette smoking, since the risk factors included in Section VIII can be influenced by cigarette smoking whereas those listed in this section are not.

Physical activity, obesity, diabetes mellitus, diet and socioeconomic factors are the risk factors which are described in this section. Each one contributes to the pathogenesis of coronary heart disease. The interplay of an individual factor with cigarette smoking is the primary concern of the discussion that follows. The general articles relating to these risk factors are contained in the following bibliographic lists:

List No. 16. Prevention of coronary risk factor.
List No. 17. Exercise in coronary heart disease.
List No. 18. Diet in the causation and prevention of coronary heart disease.

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VII-A. Physical Activity and Exercise

Physical activity and exercise relate to coronary heart disease in a number of ways. The lack of the former / is a predisposing factor, whereas exercise is a preventive one. In a patient suffering from angina pectoris, exercise initiates an attack and causes an ischemic pattern in the electrocardiogram. In a patient who has developed acute myocardial infarction, exercise properly regulated can influence the prognosis. In a patient developing coronary atherosclerosis, the electrocardiogram recorded during exercise can be helpful in the diagnosis of early insufficiency (see Additional Bibliographic List No. 17).

Cigarette smoking and exercise have been investigated jointly in regard to their influence on the prevalence of coronary heart disease. Frank et al. (1966) reviewed 301 patients with myocardial infarction who were enrolled in the Health Insurance Plan of New York. Smoking did not influence the early mortality rate (death during the first four weeks), whereas physical inactivity was associated with a high mortality rate. Morris et al. (1973) succeeded in training office workers for vigorous exercise and noted that in them the risk of developing coronary disease was about one-third that in comparable men who did not exercise. The smoking habits of men engaging in such activity were similar to those of the other men in the study. That physical working capacity is more important than cigarette smoking as a risk factor has been shown by Wilhelmsen et al. (1969).

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In elderly subjects who had vascular disease as well as in those who did not, an abnormal response to an exercise test was not associated with cigarette smoking (Riley et al., 1970). A similar lack of association was reported among businessmen undergoing a multistage exercise test (Goldbarg et al., 1970). However, in severe exercise, field testing of airmen for 12 minutes showed that endurance performance was inversely related to the number of cigarettes smoked daily (Cooper et al., 1968). There is also a reduction in endurance among long distance runners (Pyörälä et al., 1967; Haas et al., 1970) and among swimmers who are smokers (Pleasents et al., 1966). The electrocardiogram during strenuous exercise has been recorded by Berkson et al. (1966), Merriman (1967) and Recine and Chiavaro (1969). They observed that electrocardiographic changes appeared more frequently among smokers than among nonsmokers. Most of these individuals were healthy. The severity of exercise referred to above does not apply to patients with heart disease.

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VII-B. Obesity

Obesity is a major health hazard because hypertension, nephritis, diabetes, cerebrovascular disease and coronary heart disease occur more frequently in the obese (Stamler, 1959; Whyte, 1965; Stamler et al., 1960). Obesity is not an important associated risk factor in patients dying of coronary heart disease (Keys et al., 1972). Multivariate analysis of the data from 11,000 men in the United States and Europe showed that no measure of obesity made a significant contribution to future coronary heart disease when the factors of age, blood pressure, serum cholesterol and smoking were comparable. In a review of various prospective studies, Heyden et al. (1971) concluded that overweight is a definite risk factor for the development of cerebrovascular disease but not in the etiology of myocardial infarction.

In the prospective study conducted in Evans County, Georgia, the risk of nonsmokers developing coronary heart disease does not increase from the leanest to the moderately overweight and the most obese group. Among white smokers there is an increase in risk with overweight (Heyden et al., 1971). However, these results are not easy to interpret because there is a difference in body weight of smokers and nonsmokers, regardless of the status of the heart. Nonsmokers are heavier than smokers and the difference increases with age (Khosla and Lowe, 1971). Since smoking and obesity are inversely related, studies of the interrelationship of these two risk factors are needed.

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VII-C. Diabetes Mellitus and Sucrose Intake

It has been recognized for more than 35 years that diabetes mellitus predisposes the diabetic to the various manifestations of atherosclerosis, particularly coronary heart disease (Osborn and Goldstein, 1968; Hutchinson, 1970; Moller, 1970). In some of the prospective studies discussed in Section VII-E, diabetes mellitus is an important risk factor in coronary heart disease.

The combination of diabetes and cigarette smoking is suspected of increasing the hazard of the development of atherosclerosis. This has been seen in patients with arteriosclerosis obliterans (Weinroth and Herzstein, 1946; Krosnik, 1967; Kappert, 1971). However, regarding coronary heart disease among diabetics, the additional contribution of cigarette smoking to the severity of the disease has not been demonstrated by control studies. In a survey of 27,000 college alumni, cigarette smoking did not increase the risk of adult onset of diabetes and did increase the risk of coronary disease, but there was no information on the combination of the two diseases (Paffenbarger et al., 1972).

Some patients with myocardial infarction are known to have a decrease in glucose tolerance although they are not suffering from diabetes mellitus (Cohen et al., 1965; Epstein, 1967, 1969; Yudkin, 1967). The plasma-insulin level of patients with coronary heart disease is elevated, so that a deficiency of this hormone is not responsible for the decrease in glucose tolerance (Wahlberg, 1962; Nikkila et al., 1965; Peters and Hales, 1965; Welborn et al., 1966).

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In prospective studies, patients who developed coronary heart disease were found to have consumed more sugar than the control group (Paul et al., 1968; Burns-Cox et al., 1969). It is pertinent to note that in some patients with coronary heart disease there is a strong association between the consumption of sugar and the smoking of cigarettes (Medical Research Council, 1970; Bennett et al., 1970; Elwood et al., 1970). It has been suggested that both risk factors cause myocardial infarction. There is also an inverse relationship between sugar intake and adequate exercise (Richardson, 1972). Cigarette smoking is also known to influence body weight (see Section VII-B). The interplay of several risk factors should be considered when the role of sucrose in the etiology of coronary heart disease is examined in future investigations. The evidence presently available on the theory that sucrose in the diet is a major factor in the development of coronary heart disease has been reviewed by Keys (1971) and Walker (1971).

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VII-D. Diet and Coronary Heart Disease

Experiments on animals have shown that atherosclerosis, including fatal myocardial infarction, has been produced by dietary manipulation. The basic common feature in these experiments is the maintenance of a sustained elevation of the concentration of cholesterol in the blood. Epidemiological evidence indicates that in man the serum cholesterol level is a major factor in the development of coronary heart disease and that the amount and kind of fat in the serum has a major influence on the blood cholesterol level (see reviews by Keys (1962) and Stamler et al. (1963, 1972)). This knowledge has been applied in programs for the prevention of coronary heart disease, and the articles relating to dietary control are contained in Additional Bibliographic List No. 18. The controlled clinical studies by Leren (1966) and Dayton et al. (1969) are noteworthy for providing the unequivocal evidence that a diet low in unsaturated fat reduces the plasma cholesterol level and prevents complications of atherosclerosis in general and of myocardial infarction in particular.

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In the consideration of smoking and coronary heart disease the diet should also be examined. Smokers differ from nonsmokers in taste perception and food preferences. It was reported that the latter preferred bland food and consumed less fat and meat, fewer eggs and more cakes, sweets and chocolate than the former (Krut et al., 1961; Perrin et al., 1961). Among patients with myocardial infarction, liberal coffee drinking, sugar

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intake and smoking were often correlated (Kasanen and Forsström, 1966). The interplay of these dietary factors should be considered before concluding that the high incidence of smoking is the most important risk factor in patients with coronary heart disease.

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VII-E. Socioeconomic Factors

The last group of preventable risk factors are identified under the caption socioeconomic. This includes occupation, education, income level, urbanization, and consumption of alcohol, coffee and other beverages (see reviews by Terris, 1964; Anderson, 1967; Marks, 1967; Hall, 1968; Shekelle, 1968; Cheraskin et al., 1971; Richardson, 1971). Regarding the consumption of alcohol and coffee, Brummer (1969) could not find a significant correlation with coronary mortality in 20 countries. However, in isolated studies there is a correlation between the two. The studies relating to consumption of coffee and alcohol, as well as to other socioeconomic factors, are summarized in Table VII-E. It is not possible to make generalizations, because the conclusions apply only to the particular country involved and need to be confirmed elsewhere. The table has been formulated also to emphasize the interaction of cigarette smoking with socioeconomic and other risk factors in the causation of coronary heart disease. The information contained in the table has been derived from R = retrospective studies, P = prospective studies, and S = single surveys.

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The influence of cigarette smoking on prevalence of coronary heart disease in various occupational groups has been derived from surveys listed in Table VII-E. Haag and Hanmer (1957) reported a four-year survey of the mortality among employees of a tobacco company. There was a higher than average percentage of smokers associated with greater longevity and

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lower death rates from cardiovascular diseases and cancer. Their statistical techniques have been criticized by Case (1958). Most of the objections can be readily overcome by repeating the survey 15 years after it was first completed.

(Table VII-E appears on the following pages.)

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